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Claim Amendments and New Claims 32-37

Claims 1 and 31 have been amended to relate to methods of treating arthritis. Support for this amendment can be found in the specification, for example, at page 8, lines 29-30; page 9, line 21; and page 9, lines 24-27.

Claims 6, 14, 22 and 27 have been amended to recite that the chimeric antibody or chimeric fragment comprises a non-human variable region specific for tumor necrosis factor alpha or an antigen-binding portion thereof and a human constant region, as suggested by the Examiner. Support for this amendment can be found in the specification, for example, at page 15, lines 26-30.

Claims 10 and 18 have been amended to include antigen-binding fragments of the anti-TNF α antibody. Support for this amendment can be found in the specification, for example, at page 13, lines 18-22; and page 19, lines 9-13.

Claim 31 has also been amended to recite soluble TNF α receptor or functional portion thereof, wherein the soluble TNF α receptor is selected from the group consisting of p55 TNF α receptor and p75 TNF α receptor, as suggested by the Examiner. Support for this amendment can be found in the specification, for example, at page 32, lines 30-31; page 33, lines 2-7; and page 34, lines 22-26.

Claims 32 and 33, which depend from Claim 31, have been added. As discussed, Claims 32 and 33 further define the soluble TNF α receptor to be a TNF α receptor multimeric molecule (Claim 32) or a TNF α immunoreceptor fusion molecule (Claim 33). Support for Claims 32 and 33 can be found in the specification, for example, at page 33, lines 11-15; and page 33, line 22 to page 34, line 21.

In addition, as discussed, Claims 34, 35, 36 and 37, which depend from Claims 1, 10, 18 and 26, respectively, and which further define the anti-TNF α antibody or antigen-binding fragment to be a humanized anti-TNF α antibody or antigen-binding fragment thereof, have been added. Support for Claims 34-37 can be found in the specification, for example, at page 13, lines 18-22; and page 17, lines 23-28.

Paragraph 2: Priority Claim

During the interview, it was agreed that each of the pending claims was entitled to a priority date of October 8, 1992, the filing date of U.S. Application No. 07/958,248 (hereinafter referred to as "the '248 application").

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In particular, regarding Claims 5, 13 and 21, it was agreed that the objection to recitation of "multiple doses", discussed in Paper No. 20 at pages 2-3, was rendered moot by amendment of the claims to recite "a series of doses separated by intervals of days or weeks".

Regarding Claims 7-9, 15-17, 23-25 and 28-30, it was agreed that the "incorporation by reference" objection, discussed in Paper No. 20 at pages 3-4, was rendered moot in view of M.P.E.P. § 608.01(p), Part I, Section B, entitled "Review of Applications Which Are Relied On To Establish An Earlier Effective Filing Date".

Regarding Claim 31, as agreed, the claim has been amended to recite "soluble TNF α receptor", thereby rendering moot the objection to recitation of "TNF α antagonist", which was discussed in Paper No. 20 at pages 4-5.

Paragraph 4: Rejection of Claims 1-3, 5-9 and 31 Under 35 U.S.C. § 112, First Paragraph

Claims 1-3, 5-9 and 31 have been rejected under 35 U.S.C. § 112, first paragraph, because, in the Examiner's assessment, the specification does not enable any person skilled in the art to use the combination of anti-TNF α antibody and methotrexate to treat any autoimmune or inflammatory disease.

As agreed, Claims 1-3, 5-9 and 31 have been amended to relate to the treatment of arthritis, thereby rendering moot this rejection.

Paragraph 7: Rejection of Claims 1, 5-10, 13-18 and 21-31 Under 35 U.S.C. § 102(e)

Claims 1, 5-10, 13-18 and 21-31 have been rejected under 35 U.S.C. § 102(e) as being anticipated by each of the following Le *et al.* patents: U.S. Patent No. 5,656,272 (hereinafter referred to as the Le '272 patent); U.S. Patent No. 5,698,195 (hereinafter referred to as the '195 patent); and U.S. Patent No. 5,919,452 (hereinafter referred to as the '452 patent) (hereinafter referred to collectively as "the Le patents").

During the interview, the Examiner was referred to Tables 5, 6 and 12 of the Le patents, which clearly show that the patients in the clinical trials described in the Le patents were not treated with a combination of methotrexate and anti-TNF α antibody. It was also explained that the conjugates described in the Le patents (see, e.g., Le '272 patent, col. 23, para. 1; and col. 37, para. 1) do not read on Applicants' claimed invention.

The Examiner indicated that this rejection was likely overcome.

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Paragraph 8: Rejection of Claims 5 and 31 Under 35 U.S.C. § 102(e)

Claims 5 and 31 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Feldmann *et al.* (U.S. Patent No. 5,741,488; hereinafter referred to as the Feldmann '488 patent).

The Examiner indicated that this rejection was overcome in view of Applicants' arguments set forth in Amendment C, filed May 30, 2000.

Paragraph 9: Rejection of Claims 1, 5-10, 13-18 and 21-31 Under 35 U.S.C. § 102(f)

The Examiner had rejected Claims 1, 5-10, 13-18 and 21-31 under 35 U.S.C. § 102(f), stating that "it is not clear that named inventive entity Feldmann and Maini alone are the sole inventors of the claimed invention" since priority applications 07/958,248 and 08/403,785 list Feldmann, Maini and Williams as inventors and incorporate by reference the 07/943,852 application, which is a priority document of the Le patents which list Le, Vileck, Daddona, Ghrayeb, Knight and Siegel as inventors (i.e., U.S. Patent No. 5,656,272; U.S. Patent No. 5,698,195; and U.S. Patent No. 5,919,452).

This rejection was withdrawn by the Examiner in view of Applicants' arguments set forth in Amendment C.

Paragraphs 10-13: Rejections Under 35 U.S.C. § 103

Claims 1, 5-10, 13-18 and 21-31 have been rejected under 35 U.S.C. § 103 as being unpatentable over the Le '272 patent and/or the Le '195 patent and/or the Le '452 patent and Aggarwal *et al.* (U.S. Patent No. 5,672,347; hereinafter referred to as the Aggarwal '347 patent) in view of Barrera *et al.* (*Cytokine*, 3(5):504, Abstract 330 (1991)), Kozarek *et al.* (*Ann. Int. Med.*, 110:353-356 (1989)) and Markowitz *et al.* (*J. Ped. Gastroent. Nutr.*, 12:411-423 (1991)). Claims 5, 7-10, 13, 15-18, 21-25 and 28-31 have also been rejected under 35 U.S.C. § 103 as being unpatentable over the Le '272 patent and/or the Le '195 patent and/or the Le '452 patent and the Aggarwal '347 patent in view of Barrera *et al.*, Kozarek *et al.* and Markowitz *et al.* and in further view and evidence of Cohen *et al.* (*Rev. Esp. Rheumatol.*, 20(Suppl. 1):148, Abstract 318 (1993)) and Pascalis *et al.* (*Rev. Esp. Rheumatol.*, 20(Suppl. 1):148, Abstract 319 (1993)). Claims 5, 7-10, 13, 15-18, 21-25 and 28-31 have further been rejected under 35 U.S.C. § 103 as being unpatentable over the Le '272 patent and/or the Le '195 patent and/or the Le '452 patent and the Aggarwal '347 patent and/or the Feldmann '488 patent in view of Barrera *et al.*, Kozarek *et al.* and Markowitz *et al.* or in further view and evidence of Cohen *et al.* and Pascalis *et al.*

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During the interview, the Examiner was presented with an article by Verhoeven *et al.* (*British J. Rheumatol.*, 37:612-619 (1998)). Dr. Feldmann explained that Verhoeven *et al.* showed that it was not predictable whether drug combinations tested in rheumatoid arthritis show any additive or synergistic benefit. In fact, combinations of methotrexate with another drug have not been shown to have additive benefit. It was explained that results obtained with soluble TNF α receptor are expected to be similar to the results obtained with anti-TNF α antibody in light of their similar mechanism of action.

The Examiner indicated that this rejection was likely overcome for claims limited to arthritis (Claims 1, 5-9 and 31, as amended, and Claims 10 and 13-17) and claims relating to compositions comprising methotrexate and an anti-TNF α antibody (Claims 26-30).

The Examiner indicated that this rejection would likely be overcome for claims relating to treatment of Crohn's disease (Claims 18 and 21-25) with submission of evidence showing that Crohn's patients have done better with combination therapy with methotrexate and anti-TNF α antibody.

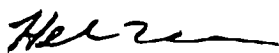
A Declaration under 37 C.F.R. § 1.132 describing the results from a study in which Crohn's patients were treated with a combination of methotrexate and anti-TNF α antibody is being prepared and will be filed as soon as it is received from the Declarant.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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